REMARKS

In the Claims:

Claims 27-34 are pending herein.

Claim Rejections under 35 U.S.C. § 101

Utility:

Claims 27-34 stand rejected under 35 U.S.C. § 101 because allegedly, the claimed invention is not supported by a substantial utility. Specifically, the Office action rejects the asserted utility as being based on a "sequence of presumptions." Page 3 of the Office action mailed January 12, 2006. According to the Office action, "[f]irst, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. The art discloses that such correlations cannot be presumed." Page 3 of the Office action mailed January 12, 2006.

Applicants respectfully disagree with this ground of rejection. Indeed, the asserted utility is not merely based on a "sequence of presumptions," but rather is based on an asserted, art-acknowledged, and demonstrated correlation between gene amplification and protein overexpression. Applicants have submitted substantial evidence, including the Goddard, Polakis, and Ashkenazi Declarations submitted previously, the second Declaration of Paul Polakis, submitted herewith, the Orntoft, Pollock, Varis, Bermont, and Hu references submitted previously, and the Papotti, Walmer, Janssens, Hahnel, Kammori, Maruyama, and Bea references submitted herewith, establishing that the correlation between gene amplification and protein overexpression is more than a presumption. This evidence clearly establishes that it is more likely than not that one of ordinary skill in the art would accept that generally, gene amplification levels correlate with protein overexpression levels.

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a

rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Office must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Indeed, an Applicant's assertion of utility is sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Significantly, statistical certainty regarding an Applicants' assertion of utility is not required to satisfy 35 U.S.C. § 101. *Nelson v. Bowler*, 626 F.2d 853, 856-857, 205 USPQ 881, 883-884 (CCPA 1980). Where an Applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed as "wrong" even where there may be some reason to question the assertion. MPEP § 2107.02. Rather, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility *violates a scientific principle or is wholly inconsistent* with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (emphasis added).

The Office action fails to overcome the presumption of truth that must be applied to Applicants' assertion of utility, *see* pages 119 and 137 of the specification, because the Office fails to establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' statement of utility. The Office action also fails to establish that Applicants' assertion of utility violates any scientific principle or that it is *wholly* inconsistent with contemporary knowledge in the art.

Indeed, it is particularly clear that the Office fails to overcome the presumption of truth that must be applied to Applicants' assertion of utility when that assertion is considered, *as it must be,* along with the substantial evidence Applicants have cited in support of the asserted utility. This substantial evidence includes the Goddard, Polakis, and

Ashkenazi Declarations submitted previously, the Second Declaration of Paul Polakis, Ph.D., submitted herewith, the Orntoft, Pollock, Varis, Bermont, and Hu references submitted previously, and the Papotti, Walmer, Janssens, Hahnel, Kammori, Maruyama, Bea, and Futcher references submitted herewith.

This evidence clearly establishes that those of skill in the art generally accept that gene expression levels correlate to protein expression levels. Indeed, paragraphs 4-6 of the Declaration of Paul Polakis, Ph.D., submitted with the Response and Request for Reconsideration mailed October 17, 2005, illustrate the art acceptance of a correlation between mRNA levels and polypeptide levels. Significantly, Dr. Polakis declares that "in approximately 80%" of the cases observed in connection with the Tumor Antigen Project, increases in the mRNA levels correlated with changes in the levels of protein expression."

However, the Office action rejects this data because, (1) the Office action alleges that the references cited in the Office action, including Pennica, Konopka, Chen, Hu, LaBaer, Hannah, Haynes, Gygi, Lian, and Fessler, provide "strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels;" (2) Dr. Polakis is employed by the assignee; and (3) "Dr Polakis refers to facts; however, the data is not included in the declaration so the examiner could not independently evaluate them." Page 8 of the Office action mailed January 12, 2006.

Applicants respectfully disagree with the above bases for rejecting the declaratory evidence of the Polakis Declaration for the following four reasons: (1) even if Dr. Polakis is employed by the assignee, he still is a qualified expert; (2) Applicants herein submit a Second Declaration of Paul Polakis, Ph.D., presenting factual data, which can be independently evaluated, demonstrating a correlation between gene amplification and protein overexpression for those genes identified in the Tumor Antigen Project; (3) numerous art references previously submitted by Applicants and those submitted herein demonstrate that a correlation between gene amplification and protein overexpression and gene amplification is art-recognized and accepted; and (4) the references cited in the

Office action do not overcome the evidence relied on by Applicants because this evidence fails to establish that it is more likely than not that in general there is no correlation between gene amplification and protein overexpression.

1. Dr. Polakis is a Qualified Expert.

Although Dr. Polakis is employed by the assignee, this is not a sufficient ground for rejecting the evidence provided by the Polakis Declaration. Indeed, Dr. Polakis's association with the assignee does not affect the fact that Dr. Polakis is clearly a qualified expert. *See, e.g.* the curriculum vitae attached to the Polakis Declaration. According to MPEP §2107, the Office "must accept an opinion from a qualified expert that is based upon relevant facts." The Office action does not dispute that the facts presented in the Polakis Declaration are relevant.

2. The Second Declaration of Paul Polakis, Ph.D. Provides Data Demonstrating Correlation Between Gene Amplification and Protein Overexpression that Can be Evaluated

Although the Office action questions the facts asserted in Dr. Polakis's Declaration because the data was not included in the declaration in a manner sufficient to allow the examiner to independently evaluate the data, Applicants herein submit a second declaration of Dr. Polakis, (*see* Exhibit 1, Second Declaration of Paul Polakis, Ph.D.). This second Polakis Declaration presents data demonstrating that more than 90% of the genes identified as being amplified in the Tumor Antigen Project referenced in the Polakis Declarations and in the Gene Amplification Experiment described in Example 28 of the specification, were detectably overexpressed in human tissue compared to normal tissue at both the mRNA and protein levels. *See* Paragraph 5 and Exhibit B of the Second Polakis Declaration. More specifically, in his second declaration, Dr. Polakis declares that the data provided therein indicates that "of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal tissue at the mRNA level, 28 of them (i.e., greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue at the protein level. As such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i)

tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." See Paragraph 5 and Exhibit B of the Second Declaration of Paul Polakis, Ph.D. (emphasis original). Thus, this declaratory evidence and data clearly establish that for the claimed polypeptide, one of ordinary skill in the art would find it more likely than not that amplification of the PRO357 nucleic acid correlates with overexpression of the PRO357 polypeptide.

3. The Majority of the Art References Establish that a General Correlation Between Gene Amplification and Protein Overexpression is Art-Recognized and Accepted

The declaratory evidence provided by the Polakis Declarations, as well as the Goddard Declaration submitted previously, is clearly consistent with the art-acceptance of a general correlation between gene amplification and protein overexpression established by the articles discussed below, including those previously cited by Applicants and the references cited herein by Applicants. Specifically, Applicants previously cited Orntoft, Pollack, Varis, Bermont, and Hu and herein cite Papotti, Walmar, Janssens, Hahnel, Kammori, Maruyama, Bea, and Futcher as establishing that Applicants' assertion of utility based on correlation between amplification of PRO357 nucleic acids and the claimed PRO357 polypeptide does not violate any scientific principles, nor is it inconsistent with the knowledge in the art. Indeed, these references establish that it is more likely than not that one of ordinary skill in the art would accept that in general there is a correlation between gene amplification and protein overexpression.

For example, Pollack *et al.* profiled DNA copy number alterations across 6,691 mapped human genes in 44 breast tumors and 10 breast cancer cell lines and reported that microarray measurements of mRNA levels revealed remarkable degrees to which variation in gene copy number contributes to variation in gene expression in tumor cells. *See* Pollack *et al.*, "Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors." 2002. *PNAS*, 99(20):12963-12968 (submitted previously). Pollack *et al* further report that their

findings that DNA copy number plays a role in gene expression levels are generalizable. Thus significantly, "[t]hese findings provide evidence that widespread DNA copy number alteration can lead directly to global deregulation of gene expression, which may contribute to the development or progression of cancer."

In particular, Pollack *et al.* report a parallel analysis of DNA copy number and mRNA levels. Pollack *et al.* found that "[t]he overall patterns of gene amplification and elevated gene expression are quite concordant, i.e., a significant fraction of highly amplified genes appear to be correspondingly highly expressed." (emphasis added). Specifically, of 117 high-level DNA amplifications 62% were associated with at least moderately elevated mRNA levels and 42% were found associated with comparably highly elevated mRNA levels.

Orntoft *et al.* report similar findings in "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics* 1.1, 37-45 (submitted previously). Initially, Orntoft *et al.* note that "[h]igh throughput array studies of the breast cancer cell line BT474 ha(ve) suggested that there is a correlation between DNA copy numbers and gene expression in highly amplified areas ( ), and studies of individual genes in solid tumors have revealed a good correlation between gene dose and mRNA or protein levels in the case of c-erb-B2, cyclin d1, ems1, and N-myc."

Specifically, Orntoft *et al.* used 2D-PAGE analysis on four breast tumor tissue samples to determine correlation between genomic and protein expression levels of 40 well resolved, known proteins. Orntoft reported that "[i[n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations ( ). Only one gene showed disagreement between transcript alteration and protein alteration." (emphasis added). Additionally, Orntoft *et al.* report that "11 chromosomal regions where CGH showed aberrations that corresponded to the changes in transcript levels also showed corresponding changes in the protein level ( )." The regions examined by Orntoft include genes encoding proteins that are often found altered in bladder cancer.

Orntoft *et al.* note that their study reports a striking correspondence between DNA copy number, mRNA expression and protein expression. Orntoft *et al.,* further note that any observed discrepancies in correlation may be attributed to translation regulation, post-translation processing, protein degradation or some combination of these. *See also* Hyman *et al.,* "Impact of DNA amplification on gene expression patterns in breast cancer." 2002. *Cancer Research*, 62:62-40-6245 (submitted previously).

Varis, Bermont, Papotti, Walmer, Janssens, Hahnel, Kammori, Maruyama, and Bea are yet further examples that utility of the present invention based on a correlation between gene amplification and protein overexpression is not wholly inconsistent with knowledge in the art. Varis et al., carried out a comprehensive analysis of gene copy number and expression levels of 636 chromosome 17-specific genes in gastric cancer. *See* Varis et al., "Targets of gene amplification and overexpression at 17q in gastric cancer." *Cancer Res.* 2002. 1;62(9):2625-9 (submitted previously). Specifically, Varis *et al.* report that analysis of DNA copy number changes by comparative genomic hybridization on a cDNA microarray revealed increased copy numbers of 11 genes, 8 of which were found to be overexpressed in the expression analysis. Thus, Varis *et al.,* teach there is a 72% correlation between increased DNA copy number and gene expression level.

Bermont teaches that overexpression of p185 is usually associated with c-erbB-2 amplification. Specifically, Bermont reports that 100% of the overexpressed p185 protein in 106 breast cancer samples studied also displayed c-erbB-2 amplification. *See* Bermont *et al.,* "Relevance of p185 HER-2/neu oncoprotein quantification in human primary breast carcinoma." *Breast Cancer Res Treat.* 2000 63(2):163-9 (submitted previously). *See also* Hu *et al.,* "Profiling of differentially expressed cancer-related genes in esophageal squamous cell carcinoma (ESCC) using human cancer cDNA arrays: overexpression of oncogene MET correlates with tumor differentiation in ESCC." *Clin Cancer Res.* 2001 7(11):3519-25 (the results of cDNA arrays showed that 13 cancer-related genes were upregulated > or = 2 fold and immunostaining results of the expression of the MET gene showed MET overexpression at the protein level, validating the cDNA arrays findings) (submitted previously).

Papotti *et al.* (*Diagn Mol Pathol.* 9(1):47-57 (2000); (submitted previously) studied the somatostatin type 2 receptor (sst2) in 26 different neuroendocrine lung tumors. They investigated mRNA levels by RT-PCR and protein levels by immunohistochemistry using 2 different antibodies. The authors report that "in the majority of samples a good correlation between sst2 mRNA (as detected by RT-PCR) and sst2 protein expression (as detected by immunohistochemistry) was observed" (Abstract). The authors also performed in situ hybridization (ISH) in selected samples which "paralleled the results obtained with the other techniques" (Abstract).

Walmer *et al.* (*Cancer Res.* 55(5):1168-75 (1995); submitted herewith) looked at lactoferrin mRNA and protein expression in endometrial adenocarcinomas and report that two thirds (8 of 12) of the samples examined overexpress lactoferrin. Walmer *et al.* also found that "this tumor-associated increase in lactoferrin expression includes an elevation in the mRNA and protein of individual cells" and that "serial sections of malignant specimens show(ed) a good correlation between the localization of lactoferrin mRNA and protein in individual epithelial cells by in situ RNA hybridization and immunohistochemistry" (Abstract).

Janssens *et al.* (*Tumour Biol.* 25(4):161-71 (2004); submitted herewith) evaluated the involvement of frizzled receptors (Fzds) in oncogenesis. They investigated mRNA expression levels in 30 different human tumor samples and their corresponding (matched) normal tissue samples by real-time quantitative PCR. Janssens *et al.* observed markedly increased Fzd5 mRNA levels in 8 of 11 renal carcinoma samples and that "Western blot analysis of crude membrane fractions revealed that Fzd5 protein expression in the matched tumor/ normal kidney samples correlated with the observed mRNA level" (Abstract).

Hahnel *et al.* (*Breast Cancer Res Treat.* 24(1):71-4 (1992); submitted herewith) studied expression of the pS2 gene in breast tissues by measuring mRNA levels using Northern blotting and protein levels by radioimmunoassay. Hahnel *et al.* indicate that "there was a

good correlation between the two measurements, indicating that expression of the pS2 gene in breast tissues may be assessed by either method."

Kammori *et al.* (*Int J Oncol.* 27:1257-63 (2005); submitted herewith) studied the expression of human telomerase reverse transcriptase (hTERT) gene and protein (besides estrogen and progesterone receptors) in breast tumors using in situ hybridization (ISH) for mRNA and immunohistochemistry (IHC) for the protein. They looked at 64 adenocarcinomas, 2 phyllode tumors and their adjacent normal breast tissues and found that hTERT mRNA was detected in 56 tumors but in neither of the 2 phyllode tumors whereas hTERT protein expression was detected by IHC in 52 tumors but in neither of the 2 phyllode tumors. The authors concluded that "there was a strong correlation between detection of hTERT gene expression by ISH and of hTERT protein by ICH in tissue specimens from breast tumors" (Abstract).

Maruyama *et al.* (*Am. J. Pathol.* 155:815-822 (1999); submitted herewith) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that all three Id mRNA species were expressed at high levels in pancreatic cancer cells as compared to normal or CP samples, and that the pancreatic cancer cell lines also exhibited "a good correlation between Id mRNA and protein levels" (Abstract). The authors measured both mRNA and protein expression in five different human pancreatic cancer cell lines. The authors observed a correlation between mRNA and protein expression of Id1 in all five cell lines, and a correlation between mRNA and protein expression for Id2 and Id3 in four out of five cell lines. In these discordant cases, Id protein levels were increased while mRNA levels were not. As noted above, Applicants make no assertions regarding changes in protein levels when mRNA levels are unchanged, nor does evidence of changes in protein levels when mRNA levels are unchanged have any relevance to Applicants' asserted utility. Thus, the authors report that increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Bea *et al.* (*Cancer Res.* 61:2409-2412 (2001); submitted herewith) investigated gene amplification, mRNA expression, and protein expression of the putative oncogene BMI-1 in lymphoma samples. The authors examined BMI-1 protein expression in 31 tumors for which levels of gene amplification and mRNA expression had been determined. Bea *et al.* found that "[a] good correlation between BMI-1 mRNA levels and protein expression was observed in all types of lymphomas" (Abstract). Thus, the authors report that increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Applicants also submit an additional reference in support of the assertion that in general, mRNA expression levels are correlated with protein expression levels. Futcher *et al.* (*Mol. Cell. Biol.* 19:7357-7368 (1999) (submitted herewith)) analyzed the yeast proteome using 2D gel electrophoresis, gathering quantitative data on protein abundance for about 1,400 spots. This data was compared to mRNA abundance for each gene as determined both by SAGE (serial analysis of gene expression) and by hybridization of cRNA to oligonucleotide arrays. The authors concluded that "several statistical methods show a strong and significant correlation between mRNA abundance and protein abundance" (page 7360, col. 2; emphasis added).

The authors note that Gygi *et al.,* cited in the Office action and discussed more fully below, completed a similar study that generated broadly similar data, but reached different conclusions. Futcher *et al.* note that this is in part a difference in viewpoint, in that "Gygi *et al.* focus on the fact that the correlations of mRNA and codon bias with protein abundance are far from perfect" (page 7367, col. 1). Applicants respectfully submit that a showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required. Applicants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predicts protein overexpression. The data of both Futcher *et al.* and Gygi *et al.* clearly meets this standard.

Futcher *et al.* also point out that "the different conclusions are also partly due to different methods of statistical analysis, and to real differences in data." Futcher *et al.* first note that

Gygi *et al.* used the Pearson product-moment correlation coefficient (rp) to measure the covariance of mRNA and protein abundance. Futcher *et al.* point out that "the rp correlation is a parametric statistic and so requires variates following a bivariate normal distribution; that is, it would be valid only if both mRNA and protein abundances were normally distributed" (page 7367, col. 1; emphasis added). As the authors disclose, "both distributions are very far from normal," and thus "a calculation of rp is inappropriate" (page 7367, col. 1).

In contrast, Futcher *et al.* used two different statistical approaches to determining the correlation between mRNA and protein abundances. First, they used the Spearman rank correlation coefficient (rs), an nonparametric statistic that does not require the data to be normally distributed. Using the rs, the authors found that mRNA abundance was well correlated with protein abundance (rs = 0.74). Applying this statistical approach to the data of Gygi *et al.* also resulted in a good correlation (rs = 0.59), although the correlation was not quite as strong as for the Futcher *et al.* data. In a second approach, Futcher *et al.* transformed the mRNA and protein data to forms where they were normally distributed, in order to allow calculation of an rp. Two types of transformation (Box-Cox and logarithmic) were used, and both resulted in good correlations between mRNA and protein abundance for Futcher *et al.*'s data.

Futcher *et al.* also note that the two studies used different methods of measuring protein abundance. Gygi *et al.* cut spots out of each gel and measured the radiation in each spot by scintillation counting, whereas Futcher *et al.* used phosphorimaging of intact gels coupled to image analysis. Futcher *et al.* point out that Gygi *et al.* may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out very small spots from the gel, and because of difficulties in background subtraction for small, weak spots. In addition, Futcher *et al.* note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong

correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher *et al.* conclude that "the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation in vivo" (page 7367, col. 2).

Accordingly, the results of Futcher *et al.* demonstrate "a strong and significant correlation between mRNA abundance and protein abundance" (page 7360, col. 2). Further, Futcher *et al.* show that when corrected for an inappropriate statistical analysis and systematic error in the measurement of low abundance proteins, the data of Gygi *et al.* also meets the "more likely than not standard" and shows that a positive correlation exists between mRNA levels and protein levels.

Thus, although there may not always be a 100% correlation between gene amplification and protein overexpression, the above-discussed references and the Polakis declarations evidence that the utility of the present invention does not violate any scientific principle, nor is it wholly inconsistent with the knowledge in the art. Indeed, these references and the declarations evidence that one of ordinary skill in the art would find it more likely than not that gene amplification of PRO357 correlates with overexpression of the PRO357 polypeptide and would accept the asserted diagnostic utility of the claimed antibodies as a specific, substantial, and credible utility.

4. The References Cited in the Office Action Fail to Establish that it is More Likely Than Not That One Of Ordinary Skill in the Art Would Find that Generally No Correlation Exists Between Gene Amplification and Protein Overexpression

The references relied on in the Office action, in rejecting the first Polakis Declaration and the references previously cited by Applicants do not satisfy the evidentiary standard required to sustain rejection of the pending claims for alleged lack of utility. Specifically, the references cited by the Office, alone or in combination, fail to establish that it is more likely than not that one of ordinary skill in the art would doubt Applicants' assertion

of a diagnostic utility of the claimed polypeptides based on the demonstrated amplification of the DNA sequences encoding those claimed polypeptides.

Specifically, Pennica *et al.* is relied on by the Office for the teaching that:

> An analysis of *WISP-1,* gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP-3* RNA was seen in the absence of DNA amplification. In contrast, *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient.

However, although the above cited passage from Pennica may illustrate that increased copy number does not *necessarily* result in increased polypeptide expression. Pennica *et al.* does not teach that no correlation can be presumed. Moreover, the standard for determining whether a correlation can be presumed is not absolute certainty. Rather, Applicants only must show that the existence of a correlation between gene amplification and protein overexpression is generally more likely than not. The fact that in Pennica, a case focused on a specific class of closely related molecules, there seemed to be no correlation with gene amplification and the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. The Office action fails to show whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . ." (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added).

More specifically, Pennica *et al.* noted that *WISPs-1* and *2* had copy numbers that were significantly higher than one, indicating gene amplification. Pennica *et al.* further noted that the copy number for *WISP-3* was "indistinguishable" from one (p=1.666), indicating no or minimal gene amplification. Next, Pennica *et al.* examined the levels of *WISP*

transcripts in RNA isolated from 19 adenocarcinomas and their matched normal mucosa using quantitative PCR. Pennica *et al.* found that *WISP-1* RNA levels displayed *good correlation* to gene amplification of *WISP-1*. Specifically, Pennica *et al.* found that RNA levels of *WISP-1* in tumor tissue were significantly increased in 84% (16/19) of the human colon tumors examined when compared with normal adjacent mucosa. *See* page 14721, Figure 7.

However, Pennica *et al.* also found that *WISP-3* RNA levels did not significantly correlate with *WISP-3* gene amplification. In particular, although *WISP-3* did not display significant gene amplification levels, RNA levels in tumor tissue were overexpressed in 63% (12/19) of the human colon tumors examined when compared with normal adjacent mucosa.

Further, Pennica *et al.* also report that *WISP-2* gene amplification levels are inversely correlated with RNA expression levels. That is, although *WISP-2* was significantly amplified, RNA levels of *WISP-2* in tumor tissues were significantly lower than RNA levels of *WISP-2* in normal adjacent mucosa. Specifically, 79% (15/19) of the samples examined displayed this expression pattern.

The Office action relies on this last result as support for the proposition that one of ordinary skill in the art would not expect gene amplification levels to correlate with protein overexpression absent explicit evidence of protein overexpression. Applicants respectfully disagree for three reasons. First, *WISP-1* gene amplification and RNA expression levels showed a significant positive correlation. Second, although *WISP-3* was not significantly amplified, it was amplified (P=1.666) and significantly overexpressed. Third, although *WISP-2* gene amplification and RNA expression levels seemed to be inversely related, Pennica *et al.* state that this result might be inaccurate. Specifically, Pennica *et al.* suggest that "[b]ecause the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." *See* 14722. Thus, because the RNA expression pattern of *WISP-2* cannot be accurately attributed to gene

amplification of *WISP-2,* this result should be disregarded. Therefore, particularly in light of the references previously cited by Applicants, and those discussed below, one of ordinary skill in the art may conclude that Pennica *et al.* supports a utility for the present invention because Pennica *et al.* teaches that gene amplification of *WISP-1* strongly correlates (84%) with RNA overexpression.

Arguably then, even considering Pennica *et al.* in the light most favorable to the Office's position, Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

The Office action also relies on Konopka *et al.,* and alleges this reference teaches that gene amplification does not correlate with protein overexpression. Applicants respectfully disagree with the Office's characterization of the teaching of Konopka and submit that the Office has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al.*, Abstract). The paper does not teach anything about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . ." is not sufficient to establish a *prima facie* case of lack of utility. It is not enough to show that for a particular gene a correlation does not exist. The law requires that the Examiner show evidence that it is more likely than not that such correlation, in general, does not exist. Such a showing has not been made.

Further, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus,

their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels.

In further support of its position, the Office action relies on Chen *et al.* and argues that Chen clearly teaches that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products . . . [and] it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples." Page 4 of the Office action mailed January 12, 2006. Although the Chen reference examines correlation between gene amplification and protein overexpression in human lung adenocarcinomas, the teachings of Chen do not make it more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility. Specifically, Chen "*suggests* that it is not possible to predict *overall* protein expression levels based on *average* mRNA abundance in lung cancer samples." Chen *et al.,* "Discordant Protein and mRNA Expression in Lung Adenocarcinomas," *Mol.& Cellular Proteomics 1.4.* 2002. 304-313, 311-12. However, Applicants' assertion of utility is not based on *overall* protein expression levels or *average* mRNA abundance in lung cancer samples. Rather, Applicants' assertion is based on the demonstrated correlation between amplification of the nucleic acids described in the specification and the polypeptides discussed in the second declaration of Paul Polakis, which is submitted herewith and discussed more fully above. Moreover, even if Chen does suggest that in general gene amplification levels cannot be used to predict protein expression levels, which Applicants expressly do not concede, Chen alone is not sufficient to overcome the teachings of the specification and the evidence submitted by Applicants.

The Office action also cites Hu *et al.* because "Hu et al discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease." Page 4 of the Office action mailed January 12, 2006. The Office action also

cites another article by an author of the Hu reference, Dr. LaBaer, for the same proposition.

However, the La Baer reference and the Hu *et al.* reference entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added), drew conclusions based upon statistical analysis of information obtained from published literature, and not from experimental data. Nowhere does either article discuss any information on microarray experiments, for example, the control used in the assays. In addition, both references have only assessed the biological significance of genes identified by microarray assay solely based on the frequency of literature citations of these genes, which does not reflect the true biological significance of these genes. Therefore, the statistical analyses by Hu *et al.,* and LaBaer are neither reliable nor informative.

The Office action further cites several references in support of the proposition that transcript levels do not correlate with polypeptide levels in normal tissues. Specifically, in support of this position, the Office action relies on references by Hanna *et al.,* Hynes *et al,* Gygi *et al.,* Lian *et al.,* and Fessler *et al.* Applicants respectfully submit that none of these references make it more likely than not that one of ordinary skill in the art would conclude that in general no correlation exists between gene amplification and protein overexpression levels.

More specifically, the Office action relies on Hanna *et al.* for the alleged teaching that "gene amplification does not reliably correlate with polypeptide overexpression, and thus, the level of polypeptide expression must be tested empirically." Page 4 of the Office action mailed January 12, 2006. However, Hanna teaches that "*[i]n general*, FISH and IHC results correlate *well*." Indeed, only for a "*subset* of tumors" were discordant results, such as protein overexpression without gene amplification or lack of protein overexpression with gene amplification, found. Thus, Hanna *et al.* teaches that generally one of ordinary skill in the art would understand gene amplification levels to correlate well with protein overexpression levels. Although there may be some

exceptions to this general rule, those exceptions do not cause the rule to violate or be inconsistent with the general scientific truth underlying the "rule" that generally gene amplification correlates well with protein overexpression.

The Office action relies on Haynes and Gygi for the proposition that abundance of mRNA expression levels does not necessarily result in increased protein expression levels. Haynes and Gygi are related references based on results obtained from "the mRNA and protein levels of a group of genes expressed in exponentially growing cells of the yeast *S. cerevisiae.*" *See* Haynes, *et al.,* "Proteome analysis: Biological assay or data archive?" *Electrophoresis,* 1998. 19:1862-1871; Gygi *et al.,* "Correlation between Protein and mRNA Abundance in Yeast," *Molecular and Cellular Biology.* 1999. 19(3): 1720-1730. Specifically, Haynes and Gygi "explore a quantitative comparison of mRNA transcript and protein levels for a relatively large number of (yeast) genes expressed in the same metabolic state." *See* Gygi *et al.,* at 1720; Haynes *et al.,* at 1862.

As an initial matter, the results of Haynes and Gygi are not relevant here because they were not obtained in a human system, did not examine any particular human gene or protein expression, and most significantly, did not examine any genes that are amplified in a cancerous state. Instead, Haynes and Gygi both examine the ability to predict protein expression levels in a *biological system.* Specifically, Haynes and Gygi examine whether there is an overall *system* correlation between gene and protein expression levels.

In contrast, the present invention involves the correlation between expression levels of a single gene, the PRO357 nucleic acid, and its encoded polypeptide. PRO357 nucleic acid is amplified in a diseased system, lung and colon tumors.

In any event, even if Haynes and Gygi were a comparable system, both report that "[f]or the entire group (106 genes) for which a complete data set was generated, there was a *general trend of increased protein levels resulting from increased mRNA levels.*" Gygi *et al.,* at 1726 (emphasis added); Haynes *et al.,* 1863. In fact, Gygi reports that the

Pearson product moment correlation coefficient for the whole data set was 0.935. Gygi *et al.,* at 1726. The Office action however, ignores this overall correlation pattern, which supports the utility of the present invention, and seizes upon a subset of genes studied in Gygi.

However, even if the general correlation taught by Haynes and Gygi is rejected, Applicants disagree that the data based on the "subset of genes" the Office action focuses on teach one of ordinary skill in the art that the present invention is not supported by a utility. Specifically, Gygi *et al.,* separate the genes studied into two groups: (1) those with a message level below 10 copies / cell in a healthy system and (2) those with more than 10 copies for cell. The Office action focuses on the first group of genes, but the second group is more relevant to the present invention, which is directed to a polypeptide encoded by an amplified nucleic acid. Indeed, this second group of genes Gygi *et al.,* studied demonstrated a high correlation between the high message levels of those genes and high protein expression levels. *See* Gygi, *et al.,* at 1726, 1727 (Figure 6). In addition, Gygi *et al.,* note that due to lower message levels in the first group (*i.e.* genes with message levels of below 10 copies / cell) "the error associated with these values (correlation between message and protein levels) may be quite large." Gygi at 1728.

Moreover, as explained more fully below, the Futcher reference discusses an analysis that is nearly identical to the analysis carried out by Gygi but reaches a different conclusion. Specifically, Futcher concludes that gene amplification levels generally are predictive of protein overexpression. As explained above, Futcher attributes this difference in conclusions to a difference in view point, use of different methods of statistical analysis, and real differences in data.

Thus, neither Haynes nor Gygi support the rejection of claims 27-34. Rather, Haynes and Gygi teach that in general there is a good correlation between message and protein levels for genes with high copy numbers per cell, which supports the asserted utility of the present invention.

In further support of the alleged lack of correlation between mRNA expression and protein expression levels, the Office action cites Lian *et al.* for the statement that there is a poor correlation between mRNA expression and protein abundance in mouse cells, and therefore it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels. Page 5 of the Office action mailed January 12, 2006

In Lian *et al.*, the authors looked at the mRNA and protein levels of genes in a derived promyelocytic mouse cell-line during differentiation of the cells from a promyelocytic stage of development to mature neutrophils following treatment with retinoic acid. The level of mRNA expression was measured using 3'-end differential display (DD) and oligonucleotide chip array hybridization to examine the expression of genes at 0, 24, 48 and 72 hours after treatment with retinoic acid. Protein levels were qualitatively assessed at 0 and 72 hours after retinoic acid treatment following 2-dimensional gel electrophoresis.

Lian *et al.* report that they were able to identify 28 proteins which they considered differentially expressed (page 521). Of those 28, only 18 had corresponding gene expression information, and only 13 had measurable levels of mRNA expression (page 521, Table 6). The authors then compared the qualitative protein level from the 2-D electrophoresis gel to the corresponding mRNA level, and reported that only 4 genes of the 18 present in the database had expression levels which were consistent with protein levels (page 521, col. 1). The authors note that "[n]one of these was on the list of genes that were differentially expressed significantly (5-fold or greater change by array or 2-fold or greater change by DD)" (page 521; emphasis added). Based on these data, the authors conclude "[f]or protein levels based on estimated intensity of Coomassie dye staining in 2DE, there was poor correlation between changes in mRNA levels and estimated protein levels" (page 522, col. 2).

The authors themselves admit that there are a number of problems with the data presented in this reference. At page 520 of this article, the authors explicitly express

their concerns by stating that "[t]hese data must be considered with several caveats: membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and proteins presented at low level will be missed. In addition, to simplify MS analysis, we used a Coomassie dye stain rather than silver to visualize proteins, and this decreased the sensitivity of detection of minor proteins." (emphasis added). It is known in the art that Coomassie dye stain is a very insensitive method of measuring protein. This suggests that the authors relied on a very insensitive measurement of the proteins studied. The conclusions based on such measurements can hardly be accurate or generally applicable. In particular, the total number of proteins examined by Lian *et al.* was only 50 (page 520, col. 2), as compared to the approximately 7000 genes for which mRNA levels were measured (page 515, col. 1). Thus, the conclusions are based on a very small and atypical set of proteins.

Applicants also emphasize that Applicants are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. As discussed above, Lian *et al.* did not take genes which showed significant mRNA changes and check the corresponding protein levels. Instead, the authors looked at a small and unrepresentative number of proteins, and checked the corresponding mRNA levels. Based on the authors' criteria, mRNA levels were significantly changed if they were at least 5-fold different when measured using a microchip array, or 2-fold different when using the more sensitive 3'-end differential display (DD). Of the 28 proteins listed in Table 6, only one has an mRNA level measured by microarray which is differentially expressed according to the authors (spot 7: melanoma X-actin, for which mRNA changed from 2539 to 341.3, and protein changed from 1 to 3). None of the other mRNAs listed in Table 6 show a significant change in expression level when using the criteria established by the authors for the less sensitive microarray technique.

There is also one gene in Table 6 whose expression was measured by the more sensitive technique of DD, and its level increased from a qualitative value of 0 to 2, a

more than 2-fold increase (spot 2: actin, gamma, cytoplasmic). This increase in mRNA was accompanied by a corresponding increase in protein level, from 3 to 6.

Therefore, although the authors characterize the mRNA and protein levels as having a "poor correlation," this does not reflect a lack of a correlation between a change in mRNA level and a corresponding change in protein level. Only two genes meet the authors' criteria for differentially expressed mRNA level, and of those, one apparently shows a corresponding change in protein level and one does not. Thus, there is little basis for the authors' conclusion that "it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels (as estimated from 2DE)."

In further support of the alleged lack of correlation between mRNA expression and protein expression levels, the Office action also cites a publication by Fessler *et al.*, as having "found a '[p]oor concordance between mRNA transcript and protein expression changes' in human cells." Page 5 of the Office action mailed January 12, 2006. Fessler is not contrary to Applicants' asserted utility, and actually supports Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. As noted above, Applicants make no assertions regarding changes in protein levels when mRNA levels are unchanged, nor does evidence of changes in protein levels when mRNA levels are unchanged have any relevance to Applicants' asserted utility.

Fessler *et al.* studied changes in neutrophil (PMN) gene transcription and protein expression following lipoplysaccharide (LPS) exposure. In Table VIII, Fessler *et al.* list a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of the 13 up-regulated proteins, a change in mRNA levels is reported for only 3 such proteins. For these 3, mRNA levels are increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels also are decreased. Thus, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants'

assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Regarding the remainder of the proteins listed in Table VIII, in 6 instances, protein levels changed while mRNA levels were unchanged. This evidence has no relevance to Applicants' assertion that changes in mRNA levels lead to corresponding changes in protein levels, since Applicants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. In the final 6 instances listed in Table VIII, protein levels changed while mRNA was noted as "absent." This evidence also has no relevance to Applicants' assertion that changes in mRNA levels causes corresponding changes in protein levels. By virtue of being "absent," it is not possible to tell whether mRNA levels were increased, decreased or remained unchanged in PMN upon contact with LPS. Nothing in these results by Fessler *et al.* suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results are not contrary to Applicants' assertions.

The Office action points to Fessler's statement regarding Table VIII that there was "a poor concordance between mRNA transcript and protein expression changes." Page 5 of the Office action mailed January 12, 2006. As is clear from the above discussion, this statement does not relate to a lack of correlation between a change in mRNA levels leading to a change in protein levels, because in 5 of 6 such instances, changes in mRNA and protein levels correlated well. Instead, this statement relates to observations in which protein levels changed when mRNA was either unchanged or "absent." As such, this statement is an observation that in addition to transcriptional activity, LPS also has post-transcriptional and possibly post-translational activity that affect protein levels, an observation which is not contrary to Applicants' assertions. Accordingly, Fessler's results are consistent with Applicants' assertion that a change in mRNA level of for a particular protein generally leads to a corresponding change in the level of the encoded protein, since 5 of 6 genes demonstrated such a correlation.

In addition to rejecting the data presented in the first Polakis Declaration and the references previously cited by Applicants, the Office action also rejects Applicants argument that the research community believes that the information obtained from gene expression chips is useful. In particular, the Office action alleges that references by Greenbaum, Winstead, and Irving illustrate that microarrays reveal little information about the encoded protein. However, none of these references, alone, in combination with each other, or in combination with the other references relied on in the Office action, establish that it is more likely than not that one of ordinary skill in the art would find that no general correlation between gene amplification and protein overexpression exists.

Indeed, the Greenbaum reference cited by the Office begins with and analyzes the art-recognized correlation between gene amplification and protein overexpression. At page 117.6, Greenbaum states "[c]orrelations have been found between mRNA expression levels of different protein subunits with protein complexes. This implies that there should be, *in general, a correlation between mRNA and protein abundance.*" Greenbaum goes on to explain that this correlation does not occur 100% of the time, likely because "a major limitation to finding correlations is the degree of natural and manufactured systematic noise in mRNA and protein expression experiments." However, this teaching is not a sufficient basis to reject Applicants' assertion of utility.

Moreover, even if Winstead and Irving illustrate that microarrays don't provide conclusive information about protein expression levels, which Applicants don't concede, for at least three reasons, these references are not sufficient to overcome the evidence submitted by Applicants demonstrating that in general one of ordinary skill in the art would find it more likely than not that gene amplification levels would correlated with protein overexpression. First, statistical certainty is not required to support Applicants' assertion. Second, Applicants used appropriate controls when measuring gene amplification, which should aid in controlling "noise" that might occur. Third, the Second Declaration of Paul Polakis, submitted herewith, provides convincing evidence that for the proteins identified in the Tumor Antigen Project, including PRO357, it is more likely than not (*i.e.* more than 90% of those tested) that gene amplification corresponds with protein overexpression.

Thus, the references relied on in the Office action do not establish that it is more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility based on a correlation between the demonstrated gene amplification and the asserted polypeptide overexpression.

Applicants respectfully submit that the Office action fails to set forth a prima facie case of lack of utility. However, even if the Office maintains that a prima facie case of lack of utility is established, consideration of the totality of the evidence, including the evidence presented by Applicants as discussed above, and the references cited by the Office, clearly demonstrates that the one of ordinary skill in the art would not find it more likely than not that, in general, there is no correlation between gene amplification and protein overexpression. Indeed, the totality of the evidence shows that the proposition that there will be correlation between protein and transcript levels does not violate any scientific principles nor is it wholly inconsistent with knowledge in the art.

Thus, although Applicants respectfully disagree with the Office's rejection of Applicants' additional asserted utility, based on the Ashkenazi Declaration submitted with Applicants' Response mailed 3 November 2003, which is supported at least by the teachings of Hanna and Mornin, *see* (Pathology Associates Medical Laboratories, August (1999), submitted herewith), Applicants need not rely on this additional asserted utility. The law only requires that an applicant provide "one credible assertion of a specific and substantial utility for each claimed invention to satisfy the utility requirement." See MPEP § 2107 (emphasis added). As explained above, Applicants have clearly established that it is more likely than not that one of ordinary skill in the art would accept that generally gene amplification correlates with protein overexpression and based on this correlation one of ordinary skill in the art would find that Applicants' assertion of utility does not violate, nor is it inconsistent with any scientific principles. Therefore, Applicants have overcome rejection of claims 27-34 for alleged lack of utility for the reasons discussed above and respectfully request that this ground of rejection be withdrawn.

35 U.S.C. § 112 ¶ 1

Enablement-Utility

The Office maintains rejection of claims 27-34 under 35 U.S.C. § 112 ¶1, alleging that because the claimed invention is not supported by either a specific asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, addressing the rejection under 35 U.S.C. § 101 for lack of utility, Applicants respectfully submit that the claimed polypeptide is supported by a specific, substantial, and credible utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 27-34 under 35 U.S.C. § 112 ¶1 for their alleged inadequate disclosure on how to use the claimed invention.

Enablement:

The Office also maintains rejection of Claims 27-34 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In particular, the Office action alleges "in view of the lack of guidance, lack of examples, and lack of predictability in the art as evidenced from the above references [cited by the Office], one skilled in the art would be forced into undue experimentation in order to practice the claimed invention." Page 14 of the Office action mailed January 12, 2006.

Applicants respectfully disagree. The specification provides significant guidance and examples. The gene amplification assay is well-described in Example 28 of the present application. Example 28 discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 10, including primary lung and colon tumors of the type and stage indicated in Table 9. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TAQMAN™ PCR. Table 10 shows the resulting gene amplification data.

Further, Example 28 explains that the results of TAQMAN™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. *See* page 120 of the specification. Thus, Table 10 demonstrates that gene amplification levels in 14 of the 15 (*i.e.* approximately 93%) lung tumor tissues listed in Table 9 and tested were greater than 2-fold. Specifically, amplification levels ranged from $2^{1.18} - 2^{3.51}$. Similarly, gene amplification levels in 12 of the 17 (*i.e.* approximately 71%) colon tumor tissues listed in Table 9 and tested were greater than 2-fold.

A change of at least 2-fold amplification relative to normal, or 1 ΔCt unit, is art recognized as indicative of significant levels of gene amplification. In support of this, Applicants respectfully direct the Examiner's attention to the Declaration of Audrey Goddard, Ph.D., submitted with the Applicants' Response mailed 3 November 2003. Dr. Goddard, an expert in the field of cancer biology and an inventor of the present invention, clearly states in her declaration that one of ordinary skill in the art would find it more likely than not that the data set forth in Table 10 at pages 125-127 of the specification indicates that the levels of PRO357 genomic DNA would be diagnostic of lung or colon cancer. Specifically, the Goddard Declaration illustrates the art acceptance of gene amplification data as an indicator of cancerous tissue.

Further, the references discussed above demonstrate that the art concerning correlation between gene amplification and protein overexpression is not unpredictable. Rather, when considered in their totality, the majority of the references discussed above, including those by Haynes, Gygi, Futcher, Fessler, Orntoft, Pollack, Varis, Bermont, Hu, Papotti, Walmar, Janssens, Hahnel, Kammori,, Maruyama, Bea, and Greenbaum establish that it is more likely than not that one of ordinary skill in the art would accept that in general a correlation between gene amplification and protein overexpression exists.

Accordingly, Applicants respectfully submit that the rejection of claims 27-34 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement is overcome and respectfully request that it be withdrawn.

Claim Rejections under 35 U.S.C. § 102(b)

The Office action rejects claims 27-34 under 35 U.S.C. § 102(b) as being anticipated by Botstein *et al.* (WO 99/35170, published 7/15/99). Anticipation under 35 U.S.C. § 102(b) requires that "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, *more than one year prior to the date of application for patent in the United States.*"

An application for a patent based on the present invention was filed at least as early as December 22, 1998, which is prior to the publication date of the cited reference. In particular, the PRO357 polypeptide and amino acid sequences are disclosed in U.S. Provisional Application Serial No. 60/113,296 ("the '296 application"), filed 12/22/1998. More specifically, the nucleic acid sequence encoding PRO357 is identified as DNA44804 and is shown in Figure 15 (SEQ ID NO:15) of the '296 application. This sequence corresponds to Figure 25 (SEQ ID NO:68) in the present application. The amino acid sequence encoding PRO357 is shown in Figure 16 (SEQ ID NO:16) of the '296 application, which corresponds to Figure 26 (SEQ ID NO:69) in the present application. In addition, the gene amplification experiment described in Example 28 of the present specification is described in Example 2 of the '296 application. For the reasons discussed above, description of the gene amplification assay in the '296 application satisfies the utility and enablement requirements.

As an application for a patent based on the present invention was filed at least as early as December 22, 1998, Applicants respectfully submit that rejection of claims 27-34 under 35 U.S.C. § 102(b) based on the Botstein reference (WO 99/3517, published 7/15/99) is improper and respectfully request that this ground of rejection be withdrawn.

Conclusion

Applicants believe that currently pending Claims 27-34 are patentable. Applicants respectfully request the Examiner grant allowance of this application. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite the prosecution this application.

Respectfully submitted,

C. Noel Kaman
Registration No. 51,857
Attorney for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200